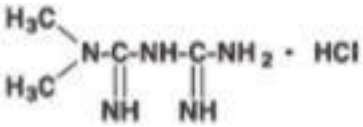
FORTAMET - metformin hydrochloride tablet, extended release
Sciele Pharma, Inc.

DESCRIPTION

FORTAMET® (metformin hydrochloride) Extended-Release Tablets contain an oral antihyperglycemic drug used in the management of type 2 diabetes. Metformin hydrochloride (N, N-dimethylimidodicarbonimidic diamide hydrochloride) is a member of the biguanide class of oral antihyperglycemics and is not chemically or pharmacologically related to any other class of oral antihyperglycemic agents. The empirical formula of metformin hydrochloride is $C_4H_{11}N_5$•HCl and its molecular weight is 165.63. Its structural formula is:



Metformin hydrochloride is a white to off-white crystalline powder that is freely soluble in water and is practically insoluble in acetone, ether, and chloroform. The pKa of metformin is 12.4. The pH of a 1% aqueous solution of metformin hydrochloride is 6.68.

FORTAMET® Extended-Release Tablets are designed for once-a-day oral administration and deliver 500 mg or 1000 mg of metformin hydrochloride. In addition to the active ingredient metformin hydrochloride, each tablet contains the following inactive ingredients: candellila wax, cellulose acetate, hypromellose, magnesium stearate, polyethylene glycols (PEG 400, PEG 8000), polysorbate 80, povidone, sodium lauryl sulfate, synthetic black iron oxides, titanium dioxide, and triacetin.

FORTAMET® meets USP Dissolution Test 5.

SYSTEM COMPONENTS AND PERFORMANCE

FORTAMET® was developed as an extended-release formulation of metformin hydrochloride and designed for once-a-day oral administration using the patented single-composition osmotic technology (SCOT™). The tablet is similar in appearance to other film-coated oral administered tablets but it consists of an osmotically active core formulation that is surrounded by a semipermeable membrane. Two laser drilled exit ports exist in the membrane, one on either side of the tablet. The core formulation is composed primarily of drug with small concentrations of excipients. The semipermeable membrane is permeable to water but not to higher molecular weight components of biological fluids. Upon ingestion, water is taken up through the membrane, which in turn dissolves the drug and excipients in the core formulation. The dissolved drug and excipients exit through the laser drilled ports in the membrane. The rate of drug delivery is constant and dependent upon the maintenance of a constant osmotic gradient across the membrane. This situation exists so long as there is undissolved drug present in the core tablet. Following the dissolution of the core materials, the rate of drug delivery slowly decreases until the osmotic gradient across the membrane falls to zero at which time delivery ceases. The membrane coating remains intact during the transit of the dosage form through the gastrointestinal tract and is excreted in the feces.

CLINICAL PHARMACOLOGY

Mechanism of Action

Metformin is an antihyperglycemic agent which improves glucose tolerance in patients with type 2 diabetes, lowering both basal and postprandial plasma glucose. Its pharmacologic mechanisms of action are different from other classes of oral antihyperglycemic agents. Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas, metformin does not produce hypoglycemia in either patients with type 2 diabetes or normal subjects (except in special circumstances, see **PRECAUTIONS**) and does not cause hyperinsulinemia. With metformin therapy, insulin secretion remains unchanged while fasting plasma insulin levels and day-long plasma insulin response may actually decrease.

PHARMACOKINETICS AND DRUG METABOLISM

Absorption and Bioavailability

The appearance of metformin in plasma from a FORTAMET® Extended-Release Tablet is slower and more prolonged compared to immediate-release metformin.

In a multiple-dose crossover study, 23 patients with type 2 diabetes mellitus were administered either FORTAMET® 2000 mg once a day (after dinner) or immediate-release (IR) metformin hydrochloride 1000 mg twice a day (after breakfast and after dinner). After 4 weeks of treatment, steady-state pharmacokinetic parameters, area under the concentration-time curve (AUC), time to peak plasma concentration (T_{max}), and maximum concentration (C_{max}) were evaluated. Results are presented in **Table 1**.

Table 1 FORTAMET® vs. Immediate-Release Metformin Steady-State Pharmacokinetic Parameters at 4 Weeks

Pharmacokinetic Parameters (mean ±SD)	**FORTAMET® 2000 mg (administered q.d.after dinner)**	**Immediate-Release Metformin 2000 mg (1000 mg b.i.d.)**
AUC_{0-24hr} (ng•hr/mL)	26,811 ± 7055	27,371 ± 5,781
T_{max} (hr)	6 (3-10)	3 (1-8)
C_{max} (ng/mL)	2849 ± 797	1820 ± 370

In four single-dose studies and one multiple-dose study, the bioavailability of FORTAMET® 2000 mg given once daily, in the evening, under fed conditions [as measured by the area under the plasma concentration versus time curve (AUC)] was similar to the same total daily dose administered as immediate-release metformin 1000 mg given twice daily. The geometric mean ratios (FORTAMET®/ immediate-release metformin) of AUC_{0-24hr}, AUC_{0-72hr}, and $AUC_{0-inf.}$ for these five studies ranged from 0.96 to 1.08.

In a single-dose, four-period replicate crossover design study, comparing two 500 mg FORTAMET® tablets to one 1000 mg FORTAMET® tablet administered in the evening with food to 29 healthy male subjects, two 500 mg FORTAMET® tablets were found to be equivalent to one 1000 mg FORTAMET® tablet.

In a study carried out with FORTAMET®, there was a dose-associated increase in metformin exposure over 24 hours following oral administration of 1000, 1500, 2000, and 2500 mg.

In three studies with FORTAMET® using different treatment regimens (2000 mg after dinner; 1000 mg after breakfast and after dinner; and 2500 mg after dinner), the pharmacokinetics of metformin as measured by AUC appeared linear following multiple-dose administration.

The extent of metformin absorption (as measured by AUC) from FORTAMET® increased by approximately 60% when given with food. When FORTAMET® was administered with food, C_{max} was increased by approximately 30% and T_{max} was more prolonged compared with the fasting state (6.1 versus 4.0 hours).

Distribution

Distribution studies with FORTAMET® have not been conducted. However, the apparent volume of distribution (V/F) of metformin following single oral doses of immediate-release metformin 850 mg averaged 654 ± 358 L. Metformin is negligibly bound to plasma proteins, in contrast to sulfonylureas, which are more than 90% protein bound. Metformin partitions into erythrocytes, most likely as a function of time. At usual clinical doses and dosing schedules of immediate-release metformin, steady state plasma concentrations of metformin are reached within 24-48 hours and are generally <1 μg/mL. During controlled clinical trials of immediate-release metformin, maximum metformin plasma levels did not exceed 5 μg/mL, even at maximum doses.

Metabolism and Excretion

Metabolism studies with FORTAMET® have not been conducted. Intravenous single-dose studies in normal subjects demonstrate that metformin is excreted unchanged in the urine and does not undergo hepatic metabolism (no metabolites have been identified in humans) nor biliary excretion.

In healthy nondiabetic adults (N=18) receiving 2500 mg q.d. FORTAMET®, the percent of the metformin dose excreted in urine over 24 hours was 40.9% and the renal clearance was 542 ± 310 mL/min. After repeated administration of FORTAMET®, there is little or no accumulation of metformin in plasma, with most of the drug being eliminated via renal excretion over a 24-hour dosing interval. The $t_{1/2}$ was 5.4 hours for FORTAMET®.

Renal clearance of metformin (**Table 2**) is approximately 3.5 times greater than creatinine clearance, which indicates that tubular secretion is the major route of metformin elimination. Following oral administration, approximately 90% of the absorbed drug is eliminated via the renal route within the first 24 hours, with a plasma elimination half-life of approximately 6.2 hours. In blood, the elimination half-life is approximately 17.6 hours, suggesting that the erythrocyte mass may be a compartment of distribution.

Special Populations

Geriatrics
Limited data from controlled pharmacokinetic studies of immediate-release metformin in healthy elderly subjects suggest that total plasma clearance of metformin is decreased, the half-life is prolonged, and C_{max} is increased, compared to healthy young subjects. From these data, it appears that the change in metformin pharmacokinetics with aging is primarily accounted for by a change in renal function (**Table 2**). FORTAMET® treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced (see **WARNINGS, PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Pediatrics
No pharmacokinetic data from studies of pediatric patients are currently available (see **PRECAUTIONS**).

Gender
Five studies indicated that with FORTAMET® treatment, the pharmacokinetic results for males and females were comparable.

Table 2 Select Mean (±SD) Metformin Pharmacokinetic Parameters Following Single or Multiple Oral Doses of Immediate-Release Metformin

Subject Groups: Immediate-Release Metformin dose[a](number of subjects)	**C_{max}b (μg/mL)**	**T_{max}c (hrs)**	**Renal Clearance (mL/min)**
Healthy, nondiabetic adults:			
500 mg single dose (24)	1.03 (±0.33)	2.75 (±0.81)	600 (±132)
850 mg single dose (74)[d]	1.60 (±0.38)	2.64 (±0.82)	552 (±139)
850 mg three times daily for 19 doses[e] (9)	2.01 (±0.42)	1.79 (±0.94)	642 (±173)
Adults with type 2 diabetes:			
850 mg single dose (23)	1.48 (±0.5)	3.32 (±1.08)	491 (±138)
850 mg three times daily for 19 doses[e] (9)	1.90 (±0.62)	2.01 (±1.22)	550 (±160)
Elderly[f], healthy nondiabetic adults:			
850 mg single dose (12)	2.45 (±0.70)	2.71 (±1.05)	412 (±98)
Renal-impaired adults:850 mg single dose			
Mild (CL_{cr}[g] 61-90 mL/min) (5)	1.86 (±0.52)	3.20 (±0.45)	384 (±122)
Moderate (CL_{cr} 31-60 mL/min) (4)	4.12 (±1.83)	3.75 (±0.50)	108 (±57)
Severe (CL_{cr} 10-30 mL/min) (6)	3.93 (±0.92)	4.01 (±1.10)	130 (±90)

[a] All doses given fasting except the first 18 doses of the multiple dose studies

[b] Peak plasma concentration

[c] Time to peak plasma concentration

[d] Combined results (average means) of five studies: mean age 32 years (range 23-59 years)

[e] Kinetic study done following dose 19, given fasting

[f] Elderly subjects, mean age 71 years (range 65-81 years)

[g] CL_{cr} = creatinine clearance normalized to body surface area of 1.73 m^2

Renal Insufficiency
In patients with decreased renal function (based on measured creatinine clearance), the plasma and blood half-life of metformin is prolonged and the renal clearance is decreased in proportion to the decrease in creatinine clearance (**Table 2**; also see **WARNINGS**).

Hepatic Insufficiency
No pharmacokinetic studies of metformin have been conducted in patients with hepatic insufficiency.

Race

No studies of metformin pharmacokinetic parameters according to race have been performed. In controlled clinical studies of immediate-release metformin in patients with type 2 diabetes, the antihyperglycemic effect was comparable in whites (n=249), blacks (n=51), and Hispanics (n=24).

Clinical Studies

In a double-blind, randomized, active-controlled, multicenter U.S. clinical study, which compared FORTAMET® q.d. to immediate-release metformin b.i.d., 680 patients with type 2 diabetes who had been taking metformin-containing medication at study entry were randomly assigned in equal numbers to double-blind treatment with either FORTAMET® or immediate-release metformin. Doses were adjusted during the first six weeks of treatment with study medication based on patients' FPG levels and were then held constant over a period of 20 weeks. The primary efficacy endpoint was the change in HbA_{1c} from baseline to endpoint. The primary objective was to demonstrate the clinical non-inferiority of FORTAMET® compared to immediate-release metformin on the primary endpoint.

FORTAMET® and metformin patients had mean HbA_{1c} changes from baseline to endpoint equal to +0.40 and +0.14, respectively (**Table 3**). The least-square (LS) mean treatment difference was 0.25 (95% CI = 0.14, 0.37) demonstrating that FORTAMET® was clinically similar to metformin according to the pre-defined criterion to establish efficacy.

Table 3 FORTAMET® vs. Immediate-Release Metformin Switch Study: Summary of Mean Changes in HbA_{1c}, Fasting Plasma Glucose, Body Weight, Body Mass Index, and Plasma Insulin

	FORTAMET®	**Immediate-Release Metformin**	**Treatment difference for change from baseline (FORTAMET® minus Immediate-Release Metformin) LS mean (2 sided 95% CI[a])**
HbA_{1c}(%)			
N	327	332	0.25
Baseline (mean ± SD)	7.04 ± 0.88	7.07 ± 0.76	(0.14,0.37)[b]
Change from baseline (mean ± SD)	0.40 ± 0.75	0.14 ± 0.75	
Fasting Plasma Glucose (mg/dL)			
N	329	333	6.43
Baseline (mean ± SD)	146.8 ± 32.1	145.6 ± 29.5	(0.57, 12.29)
Change from baseline (mean ± SD)	10.0 ± 40.8	4.2 ± 35.9	
Plasma Insulin (μu/mL)			
N	304	316	0.02
Baseline (mean ± SD)	17.9 ± 15.1	17.3 ± 10.5	(-1.47, 1.50)
Change from baseline (mean ± SD)	-3.6 ± 13.8	-3.2 ± 8.6	
Body Weight (kg)			
N	313	320	0.30
Baseline (mean ± SD)	94.1 ± 17.8	93.3 ± 17.4	(-0.22, 0.81)
Change from baseline(mean ± SD)	0.3 ± 2.9	0.0 ± 3.7	
Body Mass Index (kg/m^2)			
N	313	320	0.08
Baseline (mean ± SD)	31.1 ±4.7	31.4 ± 4.5	(-0.11, 0.26)
Change from baseline(mean ± SD)	0.1 ± 1.1	0.0 ± 1.3	

a CI= Confidence Interval

b FORTAMET® was clinically similar to immediate-release metformin based on the pre-defined criterion to establish efficacy. While demonstrating clinical similarity, the response to FORTAMET® compared to immediate-release metformin was also shown to be statistically smaller as seen by the 95% CI for the treatment difference which did not include zero.

Footnote: Patients were taking metformin-containing medications at baseline that were prescribed by their personal physician.

The mean changes for FPG (**Table 3**) and plasma insulin (**Table 3**) were small for both FORTAMET® and immediate-release metformin, and were not clinically meaningful. Seventy-six (22%) and 49 (14%) of the FORTAMET® and immediate-release patients, respectively, discontinued prematurely from the trial. Eighteen (5%) patients on FORTAMET® withdrew because of a stated lack of efficacy, as compared with 8 patients (2%) on immediate-release metformin (p=0.047).

Results from this study also indicated that neither FORTAMET® nor immediate-release metformin were associated with weight gain or increases in body mass index.

A 24-week, double blind, placebo-controlled study of immediate-release metformin plus insulin, versus insulin plus placebo, was conducted in patients with type 2 diabetes who failed to achieve adequate glycemic control on insulin alone (**Table 4**). Patients randomized to receive immediate-release metformin plus insulin achieved a reduction in HbA_{1c} of 2.10%, compared to a 1.56% reduction in HbA_{1c} achieved by insulin plus placebo. The improvement in glycemic control was achieved at the final study visit with 16% less insulin, 93.0 U/day versus 110.6 U/day, immediate-release metformin plus insulin versus insulin plus placebo, respectively, p=0.04.

Table 4 Combined Immediate-Release Metformin/lnsulin vs. Placebo/Insulin: Summary of Mean Changes from Baseline in HbA_{1c} and Daily Insulin Dose

	Immediate-Release Metformin /Insulin (n = 26)	**Placebo/Insulin (n = 28)**	**Treatment difference Mean ± SE**
HbA_{1c}(%)			
Baseline	8.95	9.32	
Change at FINAL VISIT	-2.10	-1.56	-0.54 ± 0.43[a]
Insulin Dose (U/day)			
Baseline	93.12	94.64	
Change at FINAL VISIT	-0.15	15.93	-16.08 ± 7.77[b]

[a] Statistically significant using analysis of covariance with baseline as covariate (p=0.04). Not significant using analysis of variance (values shown in table)

[b] Statistically significant for insulin (p=0.04)

A second double-blind, placebo-controlled study (n=51), with 16 weeks of randomized treatment, demonstrated that in patients with type 2 diabetes controlled on insulin for 8 weeks with an average HbA_{1c} of 7.46 ± 0.97%, the addition of immediate-release metformin maintained similar glycemic control (HbA_{1c} 7.15 ± 0.61 versus 6.97 ± 0.62 for immediate-release metformin plus insulin and placebo plus insulin, respectively) with 19% less insulin versus baseline (reduction of 23.68 ± 30.22 versus an increase of 0.43 ± 25.20 units for immediate-release metformin plus insulin and placebo plus insulin, p<0.01). In addition, this study demonstrated that the combination of immediate-release metformin plus insulin resulted in reduction in body weight of 3.11 ± 4.30 lbs, compared to an increase of 1.30 ± 6.08 lbs for placebo plus insulin, p=0.01.

Pediatric Clinical Studies

No pediatric clinical studies have been conducted with FORTAMET®. In a double-blind, placebo-controlled study in pediatric patients aged 10 to 16 years with type 2 diabetes (mean FPG 182.2 mg/dL), treatment with immediate-release metformin (up to 2000 mg/day) for up to 16 weeks (mean duration of treatment 11 weeks) resulted in a significant mean net reduction in FPG of 64.3 mg/dL compared with placebo (**Table 5**).

Table 5 Immediate-Release Metformin vs. Placebo (Pediatrics[a]): Summary of Mean Changes from Baseline* in Plasma Glucose and Body Weight at Final Visit

	Immediate-Release Metformin	**Placebo**	**p-Value**
FPG (mg/dL)	**(n = 37)**	**(n = 36)**	
Baseline	162.4	192.3	
Change at FINAL VISIT	-42.9	21.4	<0.001
Body Weight (lbs)	**(n = 39)**	**(n = 38)**	
Baseline	205.3	189.0	
Change at FINAL VISIT	-3.3	-2.0	NS**

a Pediatric patients mean age 13.8 years (range 10-16 years)

* All patients on diet therapy at Baseline

** Not statistically significant

INDICATIONS AND USAGE

FORTAMET® is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

CONTRAINDICATIONS

FORTAMET® is contraindicated in patients with:

1. Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥1.5 mg/dL [males], ≥1.4 mg/dL [females] or abnormal creatinine clearance) which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see **WARNINGS** and **PRECAUTIONS**).

2. Known hypersensitivity to metformin.

3. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma. Diabetic ketoacidosis should be treated with insulin.

FORTAMET® should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because use of such products may result in acute alteration of renal function (see also **PRECAUTIONS**).

WARNINGS

Lactic Acidosis:

Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with FORTAMET® (metformin hydrochloride) Extended-Release Tablets; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/ L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 μg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/ surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking FORTAMET® (metformin hydrochloride) Extended-Release Tablets and by use of the minimum effective dose of FORTAMET®. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. FORTAMET® treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. In addition, FORTAMET® should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, FORTAMET® should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking FORTAMET®, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, FORTAMET® should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure (see also PRECAUTIONS).

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur (see also PRECAUTIONS). FORTAMET® should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose and, if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of FORTAMET®, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking FORTAMET® do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling (see also PRECAUTIONS).

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking FORTAMET®, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions), prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery (see also CONTRAINDICATIONS and PRECAUTIONS).

PRECAUTIONS

General

Monitoring of renal function - Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of normal for their age should not receive FORTAMET®. In patisents with advanced age, FORTAMET® should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced

renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly and, generally, FORTAMET® should not be titrated to the maximum dose (see **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

Before initiation of FORTAMET® therapy and at least annually thereafter, renal function should be assessed and verified as normal. In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and FORTAMET® discontinued if evidence of renal impairment is present.

Macrovascular Outcomes -
There have been no clinical studies establishing conclusive evidence of macrovascular risk reduction with FORTAMET® or any other anti-diabetic drug.

Use of concomitant medications that may affect renal function or metformin disposition - Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion (see **PRECAUTIONS: Drug Interactions**), should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials) – Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin (see **CONTRAINDICATIONS**). Therefore, in patients in whom any such study is planned, FORTAMET® should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Hypoxic states – Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on FORTAMET® therapy, the drug should be promptly discontinued.

Surgical procedures – FORTAMET® therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids) and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol intake – Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving FORTAMET®.

Impaired hepatic function – Since impaired hepatic function has been associated with some cases of lactic acidosis, FORTAMET® should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Vitamin B_{12} levels – In controlled clinical trials of immediate-release metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12} -intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of immediate-release metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on FORTAMET® and any apparent abnormalities should be appropriately investigated and managed (see **PRECAUTIONS: Laboratory Tests**). Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels. In these patients, routine serum Vitamin B_{12} measurements at two- to three-year intervals may be useful.

Change in clinical status of patients with previously controlled type 2 diabetes – A patient with type 2 diabetes previously well controlled on FORTAMET® who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate, and metformin levels. If acidosis of either form occurs, FORTAMET® must be stopped immediately and other appropriate corrective measures initiated (see also **WARNINGS**).

Hypoglycemia – Hypoglycemia does not occur in patients receiving FORTAMET® alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking beta-adrenergic blocking drugs.

Loss of control of blood glucose – When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold FORTAMET® and temporarily administer insulin. FORTAMET® may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy. Should secondary failure occur with FORTAMET® or sulfonylurea monotherapy, combined therapy with FORTAMET® and sulfonylurea may result in a response. Should secondary failure occur with combined FORTAMET®/sulfonylurea therapy, it may be necessary to consider therapeutic alternatives including initiation of insulin therapy.

Information for Patients

Patients should be informed of the potential risks and benefits of FORTAMET® and of alternative modes of therapy. They should also be informed about the importance of adherence to dietary instructions, of a regular exercise program, and of regular testing of blood glucose, glycosylated hemoglobin, renal function, and hematologic parameters.

The risks of lactic acidosis, its symptoms, and conditions that predispose to its development, as noted in the **WARNINGS** and **PRECAUTIONS** sections, should be explained to patients. Patients should be advised to discontinue FORTAMET® immediately and to promptly notify their health practitioner if unexplained hyperventilation, myalgia, malaise, unusual somnolence, or other nonspecific symptoms occur. Once a patient is stabilized on any dose level of FORTAMET®, gastrointestinal symptoms, which are common during initiation of metformin therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Patients should be counseled against excessive alcohol intake, either acute or chronic, while receiving FORTAMET®.

FORTAMET® alone does not usually cause hypoglycemia, although it may occur when FORTAMET® is used in conjunction with oral sulfonylureas and insulin. When initiating combination therapy, the risks of hypoglycemia, its symptoms and treatment, and conditions that predispose to its development should be explained to patients and responsible family members (see **Patient Information** Printed Below).

Patients should be informed that FORTAMET® must be swallowed whole and not chewed, cut, or crushed, and that the inactive ingredients may occasionally be eliminated in the feces as a soft mass that may resemble the original tablet (see **Patient Information**).

Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of fasting blood glucose and glycosylated hemoglobin levels, with a goal of decreasing these levels toward the normal range. During initial dose titration, fasting glucose can be used to determine the therapeutic response. Thereafter, both glucose and glycosylated hemoglobin should be monitored. Measurements of glycosylated hemoglobin may be especially useful for evaluating long-term control (see also **DOSAGE AND ADMINISTRATION**).

Initial and periodic monitoring of hematologic parameters (e.g., hemoglobin/hematocrit and red blood cell indices) and renal function (serum creatinine) should be performed, at least on an annual basis. While megaloblastic anemia has rarely been seen with immediate-release metformin therapy, if this is suspected, Vitamin B_{12} deficiency should be excluded.

Drug Interactions (Clinical Evaluation of Drug Interactions Conducted with Immediate-Release Metformin)

Glyburide– In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The single-dose nature of this study and the lack of correlation between glyburide blood levels and pharmacodynamic effects, makes the clinical significance of this interaction uncertain (see **DOSAGE AND ADMINISTRATION: Concomitant FORTAMET® and Oral Sulfonylurea Therapy in Adult Patients**).

Furosemide– A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine– A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount

excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs– Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose, metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of FORTAMET® and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other– Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, and isoniazid. When such drugs are administered to a patient receiving FORTAMET®, the patient should be closely observed for loss of blood glucose control. When such drugs are withdrawn from a patient receiving FORTAMET®, the patient should be observed closely for hypoglycemia.

In healthy volunteers, the pharmacokinetics of metformin and propranolol, and metformin and ibuprofen were not affected when co-administered in single-dose interaction studies.

Metformin is negligibly bound to plasma proteins and is, therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol, and probenecid, as compared to the sulfonylureas, which are extensively bound to serum proteins.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term carcinogenicity studies with metformin have been performed in rats (dosing duration of 104 weeks) and mice (dosing duration of 91 weeks) at doses up to and including 900 mg/kg/day and 1500 mg/kg/day, respectively. These doses are both approximately four times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons. No evidence of carcinogenicity with metformin was found in either male or female mice. Similarly, there was no tumorigenic potential observed with metformin in male rats. There was, however, an increased incidence of benign stromal uterine polyps in female rats treated with 900 mg/kg/day.

There was no evidence of mutagenic potential of metformin in the following *in vitro* tests: Ames test (*S. typhimurium*), gene mutation test (mouse lymphoma cells), or chromosomal aberrations test (human lymphocytes). Results in the *in vivo* mouse micronucleus test were also negative.

Fertility of male or female rats was unaffected by metformin when administered at doses as high as 600 mg/kg/day, which is approximately three times the maximum recommended human daily dose based on body surface area comparisons.

Pregnancy

Teratogenic Effects: Pregnancy Category B

Recent information strongly suggests that abnormal blood glucose levels during pregnancy are associated with a higher incidence of congenital abnormalities. Most experts recommend that insulin be used during pregnancy to maintain blood glucose levels as close to normal as possible. Because animal reproduction studies are not always predictive of human response, FORTAMET® should not be used during pregnancy unless clearly needed.

There are no adequate and well-controlled studies in pregnant women with immediate-release metformin or FORTAMET®. Metformin was not teratogenic in rats and rabbits at doses up to 600 mg/kg/day. This represents an exposure of about two and six times the maximum recommended human daily dose of 2000 mg based on body surface area comparisons for rats and rabbits, respectively. Determination of fetal concentrations demonstrated a partial placental barrier to metformin.

Nursing Mothers

Studies in lactating rats show that metformin is excreted into milk and reaches levels comparable to those in plasma. Similar studies have not been conducted in nursing mothers. Because the potential for hypoglycemia in nursing infants may exist, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. If FORTAMET® is discontinued, and if diet alone is inadequate for controlling blood glucose, insulin therapy should be considered.

Pediatric Use

No pediatric clinical studies have been conducted with FORTAMET®. The safety and effectiveness of immediate-release metformin for the treatment of type 2 diabetes have been established in pediatric patients ages 10 to 16 years (studies have not been conducted in pediatric patients below the age of 10 years). Use of immediate-release metformin in this age group is supported by evidence from adequate and well-controlled studies of immediate-release metformin in adults with additional data from a controlled clinical study in pediatric patients ages 10-16 years with type 2 diabetes, which demonstrated a similar response in glycemic control to that seen in adults (see **CLINICAL PHARMACOLOGY: Pediatric Clinical Studies**). In this study, adverse effects were similar to those described in adults (see **ADVERSE REACTIONS: Pediatric Patients**). A maximum daily dose of 2000 mg of immediate-release metformin is recommended.

The safety and efficacy of FORTAMET® has not been evaluated in pediatric patients.

Geriatric Use

Of the 389 patients who received FORTAMET® in controlled Phase III clinical studies, 26.5% [103/389] were 65 years and older. No overall differences in effectiveness or safety were observed between these patients and younger patients.
Controlled clinical studies of immediate-release metformin did not include sufficient numbers of elderly patients to determine whether they respond differently from younger patients, although other reported clinical experience has not identified differences in responses between the elderly and younger patients. Metformin is known to be substantially excreted by the kidney and because of the risk of serious adverse reactions to the drug is greater in patients with impaired renal function, immediate-release metformin should only be used in patients with normal renal function (see **CONTRAINDICATIONS**, **WARNINGS**, and **CLINICAL PHARMACOLOGY: Pharmacokinetics**). Because aging is associated with reduced renal function, immediate-release metformin should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function. Generally, elderly patients should not be titrated to the maximum dose of immediate-release metformin (see also **WARNINGS** and **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS

FORTAMET® Clinical Studies

In the controlled clinical studies of FORTAMET® in patients with type 2 diabetes, a total of 424 patients received FORTAMET® therapy (up to 2500 mg/day) and 430 patients received immediate-release metformin. Adverse reactions reported in ≥5% of the FORTAMET® or immediate-release metformin patients are listed in **Table 6**. These pooled results show that the most frequently reported adverse reactions in the FORTAMET® group were infection, diarrhea, and nausea. Similar incidences of these adverse reactions were seen in the immediate-release metformin group.

Table 6 Number and Percentage of Patients With the Most Common (Incidence ≥5%)Treatment-Emergent Signs or Symptoms by Body System and Preferred Term - Pooled Phase II and III Studies

	FORTAMET® (N=424)		**Immediate-Release Metformin (N=430)**	
Body System Preferred Term	**n**	**(%)**	**n**	**(%)**
Body as a Whole				
Accidental Injury	31	(7.3)	24	(5.6)
Headache	20	(4.7)	22	(5.1)
Infection	87	(20.5)	90	(20.9)
Digestive System				
Diarrhea	71	(16.7)	51	(11.9)
Dyspepsia	18	(4.2)	22	(5.1)
Nausea	36	(8.5)	32	(7.4)
Respiratory System				
Rhinitis	18	(4.2)	24	(5.6)

The most frequent adverse events thought to be related to FORTAMET® were diarrhea, nausea, dyspepsia, flatulence, and abdominal pain. The frequency of dyspepsia was 4.2% in the FORTAMET® group compared to 5.1% in the immediate-release group, the frequency of flatulence was 3.5% in the FORTAMET® group compared to 3.7% in the immediate-release group, and the frequency of abdominal pain was 3.3% in the FORTAMET® group compared to 4.4% in the immediate-release group.

In the controlled studies, 4.7% of patients treated with FORTAMET® and 4.9% of patients treated with immediate-release metformin were discontinued due to adverse events.

Immediate-Release Metformin

Immediate-Release Metformin Phase III Clinical Studies

In a U.S. double-blind clinical study of immediate-release metformin in patients with type 2 diabetes, a total of 141 patients received immediate-release metformin therapy (up to 2550 mg per day) and 145 patients received placebo. Adverse reactions reported in greater than 5% of the immediate-release metformin patients, and that were more common in immediate-release metformin than placebo-treated patients, are listed in **Table 7.**

Table 7 Most Common Adverse Reactions (>5.0%) in a Placebo-Controlled Clinical Study of Immediate-Release Metformin Monotherapy*

	Immediate-Release Metformin Monotherapy (n = 141)	**Placebo (n = 145)**
Adverse Reaction	**% of Patients**	
Diarrhea	53.2	11.7
Nausea/Vomiting	25.5	8.3
Flatulence	12.1	5.5
Asthenia	9.2	5.5
Indigestion	7.1	4.1
Abdominal Discomfort	6.4	4.8
Headache	5.7	4.8

* Reactions that were more common in immediate-release metformin than placebo-treated patients

Diarrhea led to discontinuation of study medication in 6% of patients treated with immediate-release metformin. Additionally, the following adverse reactions were reported in ≥1.0 - ≤5.0% of immediate-release metformin patients and were more commonly reported with immediate-release metformin than placebo: abnormal stools, hypoglycemia, myalgia, lightheaded, dyspnea, nail disorder, rash, sweating increased, taste disorder, chest discomfort, chills, flu syndrome, flushing, palpitation.

Pediatric Patients

No pediatric clinical studies have been conducted with FORTAMET®. In clinical trials with immediate-release metformin in pediatric patients with type 2 diabetes, the profile of adverse reactions was similar to that observed in adults.

OVERDOSAGE

Hypoglycemia has not been seen even with ingestion of up to 85 grams of immediate-release metformin, although lactic acidosis has occurred in such circumstances (see **WARNINGS**). Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin over-dosage is suspected.

DOSAGE AND ADMINISTRATION

There is no fixed dosage regimen for the management of hyperglycemia in patients with type 2 diabetes with FORTAMET® or any other pharmacologic agent. Dosage of FORTAMET® must be individualized on the basis of both effectiveness and tolerance, while not exceeding the maximum recommended daily dose. The maximum recommended daily dose of FORTAMET® Extended-Release Tablets in adults is 2500 mg.

FORTAMET® should be taken with a full glass of water once daily with the evening meal. FORTAMET® should be started at a low dose, with gradual dose escalation, both to reduce gastrointestinal side effects and to permit identification of the minimum dose required for adequate glycemic control of the patient.

During treatment initiation and dose titration (see **Recommended Dosing Schedule**), fasting plasma glucose should be used to determine the therapeutic response to FORTAMET® and identify the minimum effective dose for the patient. Thereafter, glycosylated hemoglobin should be measured at intervals of approximately three months. The therapeutic goal should be to decrease both fasting plasma glucose and glycosylated hemoglobin levels to normal or near normal by using the lowest effective dose of FORTAMET®, either when used as monotherapy or in combination with sulfonylurea or insulin.

Monitoring of blood glucose and glycosylated hemoglobin will also permit detection of primary failure, i.e., inadequate lowering of blood glucose at the maximum recommended dose of medication, and secondary failure, i.e., loss of an adequate blood glucose lowering response after an initial period of effectiveness.

Short-term administration of FORTAMET® may be sufficient during periods of transient loss of control in patients usually well-controlled on diet alone.

Recommended Dosing Schedule

The usual starting dose of FORTAMET® (metformin hydrochloride) Extended-Release Tablets is 1000 mg taken with a full glass of water once daily with the evening meal, although 500 mg may be utilized when clinically appropriate. Dosage increases should be made in increments of 500 mg weekly, up to a maximum of 2500 mg once daily with the evening meal (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

In randomized trials, patients currently treated with immediate-release metformin were switched to FORTAMET®. Results of this trial suggest that patients receiving immediate-release metformin treatment may be safely switched to FORTAMET® once daily at the same total daily dose, up to 2500 mg once daily. Following a switch from immediate-release metformin to FORTAMET®, glycemic control should be closely monitored and dosage adjustments made accordingly (see **CLINICAL PHARMACOLOGY, Clinical Studies**).

Pediatrics – There is no pediatric information available for FORTAMET®.

Transfer From Other Antidiabetic Therapy

When transferring patients from standard oral hypoglycemic agents other than chlorpropamide to FORTAMET®, no transition period generally is necessary. When transferring patients from chlorpropamide, care should be exercised during the first two weeks because of the prolonged retention of chlorpropamide in the body, leading to overlapping drug effects and possible hypoglycemia.

Concomitant FORTAMET® and Oral Sulfonylurea Therapy in Adult Patients

If patients have not responded to four weeks of the maximum dose of FORTAMET® monotherapy, consideration should be given to gradual addition of an oral sulfonylurea while continuing FORTAMET® at the maximum dose, even if prior primary or secondary failure to a sulfonylurea has occurred. Clinical and pharmacokinetic drug-drug interaction data are currently available only for metformin plus glyburide (also known as glibenclamide). With concomitant FORTAMET® and sulfonylurea therapy, the desired control of blood glucose may be obtained by adjusting the dose of each drug. However, attempts should be made to identify the minimum effective dose of each drug to achieve this goal. With concomitant FORTAMET® and sulfonylurea therapy, the risk of hypoglycemia associated with sulfonylurea therapy continues and may be increased. Appropriate precautions should be taken (see Package Insert of the respective sulfonylurea).

If patients have not satisfactorily responded to one to three months of concomitant therapy with the maximum dose of FORTAMET® and the maximum dose of an oral sulfonylurea, consider therapeutic alternatives including switching to insulin with or without FORTAMET®.

Concomitant FORTAMET® and Insulin Therapy in Adult Patients

The current insulin dose should be continued upon initiation of FORTAMET® therapy. FORTAMET® therapy should be initiated at 500 mg once daily in patients on insulin therapy. For patients not responding adequately, the dose of FORTAMET® should be increased by 500 mg after approximately 1 week and by 500 mg every week thereafter until adequate glycemic control is achieved. The maximum recommended daily dose for FORTAMET® Extended-Release Tablets is 2500 mg. It is recommended that the insulin dose be decreased by 10% to 25% when fasting plasma glucose concentrations decrease to less than 120 mg/dL in patients receiving concomitant insulin and FORTAMET®. Further adjustment should be individualized based on glucose-lowering response.

Specific Patient Populations

FORTAMET® is not recommended for use in pregnancy, and is not recommended in patients below the age of 17 years.

The initial and maintenance dosing of FORTAMET® should be conservative in patients with advanced age, due to the potential for decreased renal function in this population. Any dosage adjustment should be based on a careful assessment of renal function. Generally, elderly, debilitated, and malnourished patients should not be titrated to the maximum dose of FORTAMET®.

Monitoring of renal function is necessary to aid in prevention of lactic acidosis, particularly in the elderly (see **WARNINGS**).

HOW SUPPLIED

FORTAMET® (metformin hydrochloride) Extended-Release Tablets are supplied as biconvex-shaped, film-coated extended-release tablets containing 500 mg or 1000 mg of metformin hydrochloride.
NDC 59630-574-60: 500 mg extended-release, white-colored tablets imprinted with Andrx logo and 574 on one side: bottles of 60.

NDC 59630-575-60: 1000 mg extended-release, white-colored tablets imprinted with Andrx logo and 575 on one side: bottles of 60.

STORAGE

Store at 20-25°C (68-77°F) - Excursions permitted to 15° - 30°C (59° - 86°F) [See USP Controlled Room Temperature]. Keep tightly closed (protect from moisture). Protect from light. Avoid excessive heat and humidity.

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PATIENT INFORMATION ABOUT FORTAMET®
(metformin hydrochloride) Extended-Release Tablets

Q1. Why do I need to take FORTAMET®?

Your doctor has prescribed FORTAMET® to treat your type 2 diabetes, a condition in which blood sugar (blood glucose) is elevated. There are two types of diabetes. FORTAMET® is indicated for the most common type, known as type 2 diabetes.

Q2. Why is it important to control type 2 diabetes?

Type 2 diabetes has multiple possible complications, including blindness, kidney failure, and circulatory and heart problems. Lowering your blood sugar to a normal level may prevent or delay these complications.

Q3. How is type 2 diabetes usually controlled?

High blood sugar can be lowered by diet and exercise, by a number of oral medications and by insulin injections. Your doctor may recommend that you try lifestyle modifications such as improved diet and exercise before initiating drug treatment for type 2 diabetes. Each patient will be treated individually by his or her physician, and should follow all treatment recommendations.

Q4. Does FORTAMET® work differently from other glucose control medications?

Yes. FORTAMET®, as well as other formulations of metformin, lowers the amount of sugar in your blood by controlling how much sugar is released by the liver. FORTAMET® (metformin hydrochloride) does not cause your body to produce more insulin. FORTAMET® rarely causes hypoglycemia (low blood sugar) and it does not usually cause weight gain when taken alone. However, if you do not eat enough, if you take other medications to lower blood sugar, or if you drink alcohol, you can develop hypoglycemia. Specifically, when FORTAMET® is taken together with a sulfonylurea or with insulin, hypoglycemia and weight gain are more likely to occur.

Q5. What happens if my blood sugar is still too high?

If your blood sugar is high, consult your physician. When blood sugar cannot be lowered enough by either FORTAMET® (metformin hydrochloride) Extended-Release Tablets or a sulfonylurea, the two medications can be effective when taken together. Other alternatives involve switching to other oral antidiabetic drugs (e.g., alpha glucoside inhibitors or glitazones). FORTAMET® may be stopped and replaced with other drugs and/or insulin. If you are unable to maintain your blood sugar with diet, exercise and glucose-control medications taken orally, then your doctor may prescribe injectable insulin to control your diabetes.

Q6. Why should I take FORTAMET® in addition to insulin if I am already on insulin alone?

Adding FORTAMET® to insulin can help you better control your blood sugar while reducing the insulin dose and possibly reducing your weight.

Q7. Can FORTAMET® cause side effects?

FORTAMET®, like all blood sugar-lowering medications, can cause side effects in some patients. Most of these side effects are minor and will go away after you've taken FORTAMET® for a while. However, there are also serious but rare side effects related to FORTAMET® (see below).

Q8. What kind of side effects can FORTAMET® cause?

If side effects occur, they usually occur during the first few weeks of therapy. They are normally minor ones such as diarrhea, nausea, abdominal pain and upset stomach. FORTAMET® is generally taken with meals, which reduce these side effects.
Although these side effects are likely to go away, call your doctor if you have severe discomfort or if these effects last for more than a few weeks. Some patients may need to have their doses lowered or stop taking FORTAMET®, either temporarily or permanently. You should tell your doctor if the problems come back or start later on during the therapy.

WARNING: A rare number of people who have taken metformin have developed a serious condition called lactic acidosis.

Properly functioning kidneys are needed to help prevent lactic acidosis. You should not take FORTAMET® if you have impaired kidney function, as measured by a blood test (see Q9-13).

Q9. Are there any serious side effects that FORTAMET® can cause?

FORTAMET® rarely causes serious side effects. The most serious side effect that FORTAMET® can cause is called lactic acidosis.

Q10. What is lactic acidosis and can it happen to me?

Lactic acidosis is caused by a build-up of lactic acid in the blood. Lactic acidosis associated with metformin is rare and has occurred mostly in people whose kidneys were not working normally. Lactic acidosis has been reported in about one in 33,000 patients taking metformin over the course of a year. Although rare, if lactic acidosis does occur, it can be fatal in up to half the cases.

It is also important for your liver to be working normally when you take FORTAMET®. Your liver helps to remove lactic acid from your bloodstream. Your doctor will monitor your diabetes and may perform blood tests on you from time to time to make sure your kidneys and your liver are functioning normally. There is no evidence that FORTAMET® causes harm to the kidneys or liver.

Q11. Are there other risk factors for lactic acidosis?

Your risk of developing lactic acidosis from taking FORTAMET® is very low as long as your kidneys and liver are healthy. However, some factors can increase your risk because they can affect kidney and liver function. You should discuss your risk with your physician. You should not take FORTAMET® if:

- You have some forms of kidney or liver problems
- You have congestive heart failure which is treated with medications, e.g., digoxin (Lanoxin®) or furosemide (Lasix®)
- You drink alcohol excessively (all the time or short-term “binge” drinking)
- You are seriously dehydrated (have lost a large amount of body fluids)
- You are going to have, within a few days, certain x-ray tests with injectable contrast agents
- You are going to have surgery
- You develop a serious condition such as a heart attack, severe infection, or a stroke
- You are 80 years of age or older and have NOT had your kidney function tested

Q12. What are the symptoms of lactic acidosis?

Some of the symptoms include feeling very weak, tired or uncomfortable, unusual muscle pain, trouble breathing, unusual or unexpected stomach discomfort, feeling cold, feeling dizzy or lightheaded, or suddenly developing a slow or irregular heartbeat. If you notice these symptoms, or if your medical condition has suddenly changed, stop taking FORTAMET® and call your doctor right away. Lactic acidosis is a medical emergency that must be treated in a hospital.

Q13. What does my doctor need to know to decrease my risk of lactic acidosis?

Tell your doctor if you have an illness that results in severe vomiting, diarrhea and/or fever, or if your intake of fluids is generally reduced. These situations can lead to severe dehydration, and it may be necessary to stop taking FORTAMET® temporarily. You should let your doctor know if you are going to have any surgery or specialized x-ray procedures that require injection of contrast agents. FORTAMET® therapy will need to be stopped temporarily in such instances.

Q14. Can I take FORTAMET® with other medications?

Remind your doctor and/or pharmacist that you are taking FORTAMET® when any new drug is prescribed or a change is made in how you take a drug already prescribed. FORTAMET® may interfere with the way some drugs work and some drugs may interfere with the action of FORTAMET®.

Q15. What if I become pregnant while taking FORTAMET®?

Tell your doctor if you plan to become pregnant or have become pregnant. As with other oral glucose-control medications, you should not take FORTAMET® during pregnancy. Usually your doctor will prescribe insulin while you are pregnant.

Q16. How do I take FORTAMET®?

FORTAMET® tablets should not be cut, crushed, or chewed and should be taken whole with a full glass of water once daily with the evening meal. Occasionally, the inactive ingredients of FORTAMET® may be eliminated as a soft mass in your stool that may look like the original tablet; this is not harmful and will not effect the way FORTAMET® works to control diabetes. FORTAMET® should be taken once a day with food. You will be started on a low dose of FORTAMET® and your dosage will be increased gradually until your blood sugar is controlled.

Q17. Where can I get more information about FORTAMET®?

This leaflet is a summary of the most important information about FORTAMET®. If you have any questions or problems, you should talk to your doctor or other healthcare provider about type 2 diabetes as well as FORTAMET® and its side effects.

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